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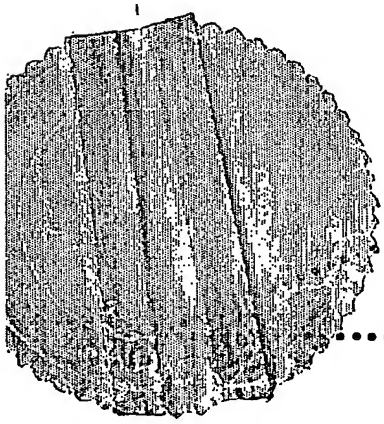
Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 25/11/2003 in respect of Patent Application No.1217/MUM/2003 of CADILA HEALTHCARE LIMITED, a company incorporated under the Companies Act, 1956 of Zydus Research Centre, Zydus Towers, Satellite Cross Road, Ahmedabad – 380 015, Gujarat, India.

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act, 1970.



Dated this 24th day of January 2005.

(R.BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF PATENT
(See Sections 5(2), 7, 54 and 135 AND Rule 39)

(1) We, **CADILA HEALTHCARE LTD**, a company incorporated under the Companies Act, 1956 of Zydus Research Centre, Zydus Towers, Satellite Cross Road, Ahmedabad-380 015, Gujarat, India .

(2) hereby declare –

(a) We are in possession of an invention titled.

"IMPROVED PROCESS FOR THE PREPARATION OF FORM I OF (S)-(+)-CLOPIDOGREL"

(b) Provisional Specification relating to this invention is filed with this application;

(c) that there is no lawful ground of objection to the grant of a patent to us.

(3) further declare that the inventors for the said invention are:

(1) **LOHRAY, Braj, Bhushan**, an Indian citizen, of CADILA HEALTHCARE LIMITED, Zydus Towers, Satellite Cross Road, Ahmedabad-380 015, Gujarat, India

(2) **LOHRAY, Vidya, Bhushan,** an Indian citizen, of CADILA HEALTHCARE LIMITED, Zydus Towers, Satellite Cross Road, Ahmedabad-380 015, Gujarat, India

(3) **DAVE, Mayank, Ghanshyambhai,** an Indian citizen of CADILA HEALTHCARE LIMITED, Zydus Towers, Satellite Cross Road, Ahmedabad-380 015, Gujarat, India

(4) We claim priority from the application(s) filed in the following convention country, particulars of which are as follows: ***NIL***

(5) That we are the assignees of the true and first inventors.

(6) That our address for service in India is as follows;

SUBRAMANIAM, NATARAJ & ASSOCIATES
Attorneys-at-Law
E 556, Greater Kailash II,
New Delhi - 110 048, India.
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(7) The following declaration was given by the true and first inventors:

We, **LOHRAY, Braj, Bhushan; LOHRAY, Vidya, Bhushan; DAVE, Mayank Ghanshyambhai;** all Indian citizens, of CADILA HEALTHCARE LIMITED, Zydus Towers, Satellite Cross Road, Ahmedabad-380 015, Gujarat, India; the true and first inventors declare the applicants herein are our assignees:

DUPLICATE

1217/मुंबई/MUM/2003

25 NOV 2003

Braj Bhushan. LOHRAY

Vidya Bhushan. LOHRAY

Mayank Ghanshyambhai DAVE

(8) that to the best of our knowledge, information and belief the facts and matters stated herein are correct and there is no lawful ground of objection to the grant of patent to me/us on this application.

(9) Following are the attachments with this application:

(a) PROVISIONAL specification in duplicate
(b) Form 1 in duplicate
(c) Form 2 in duplicate
(d) Statement and Undertaking on FORM 3 in duplicate

Fee Rs. ..... in Cash/Cheque/Bank Draft Bearing No.....
dated..... On .....Bank.

We request that a patent be granted to us for the said invention.

Dated this the 24th day of November 2003

CADILA HEALTHCARE LIMITED

The Controller of Patents
The Patent Office,
At Mumbai

Form 2

THE PATENTS ACT, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION
(Section 10; rule 13)

"Improved process for the preparation of form I of (S)-(+)-Clopidogrel Bisulfate"

DUPLICATE

Cadila Healthcare Limited, a company incorporated under the Companies Act, 1956, of Zydus Research Centre, Zydus Tower, Satellite Cross Road, Ahmedabad 308 015, Gujarat, India

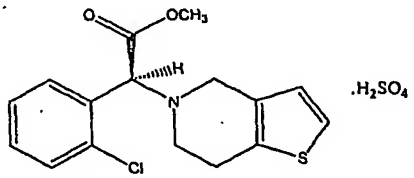
The following specification describes the nature of the invention:

FIELD OF INVENTION

The present invention describes improved processes for the preparation of Form I of *(S)*-(+)-Clopidogrel bisulfate. The present invention also reveals various pharmaceutical compositions containing the Form I prepared according to the present invention. (*S*)-(+)-Clopidogrel bisulfate an antiplatelet drug is currently being marketed for the treatment of atherosclerosis, myocardial infraction, strokes and vascular death.

BACKGROUND OF THE INVENTION

Clopidogrel bisulfate corresponds to the empirical formula $C_{16}H_{16}ClNO_2S.H_2SO_4$ and has a molecular weight 419.9. Chemically it is methyl (+)-*(S)*-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate (1:1), having the following structural formula.



Clopidogrel is an inhibitor of platelet aggregation and is marketed as an antianginal agent, antiplatelet agent and is found to decrease morbid events in people with established atherosclerotic cardiovascular disease and cerebrovascular diseases.

The therapeutic application of Clopidogrel as blood-platelet aggregation inhibiting agents and antithrombotic agent and its preparation is disclosed in U.S. Patent No. 4,529,596.

US Patent No 4,847,265 describes the process for the preparation of the hydrogen sulfate salt of Clopidogrel.

Various other strategies to prepare Clopidogrel are disclosed in WO 98/51681, WO 98/51682, WO 98/51689, WO 99/18110, US 5,036,156, US 5,132, 435, US 5,139,170, US 5,204,469 and US 6,080,875.

US Patent No. 4,847,265 discloses that the dextrorotatory enantiomer of formula (I) of Clopidogrel has an excellent antiagregant platelet activity, whereas the corresponding levorotatory enantiomer of (I) is less tolerated of the two enantiomers and is less active. US Patent No. 4,847,265 relates to the dextrorotatory enantiomer and its pharmaceutically acceptable salts with platelet aggregation inhibiting activity. However, the precision of

determination of levocnantiomer in dextrorotatory enantiomer was not less than 4 %, implying thereby that the method used by the inventors cannot distinguish precisely a sample of S:R ratio 96:4 from a sample having the two enantiomers in the ratio 99.5:0.5 (*refer page 5, line 35-50, Patent No US 4,847,265*). Current regulatory requirements, however, require a high chiral purity (e.e. not less than 99%) for chiral drugs.

Subsequently filed Patent Application WO 99/65915 (US 6,429,210) titled "Polymorphic Clopidogrel hydrogensulfate form", which is herein incorporated by reference, discloses the existence of a specific polymorphic Form II of the hydrogen sulfate of (*S*)-(+)-Clopidogrel (m.p. = 176 ± 3 °C). It is also disclosed in this patent application that the earlier processes described in the U.S. Patent 4,847,265 gives Form I (m.p. 184 ± 3 °C). These two crystalline polymorphic forms I and II differed in their stability, physical properties, spectral characteristics and their method of preparation. However, both the polymorphs have similar bioavailability, as shown in their bioequivalence in healthy human volunteers.

Although U.S. patent No. 4,847,265 reports the formation of (*S*)-(+)-Clopidogrel bisulfate salt with m.p. 184 °C, it was disclosed as Form I only in patent application WO 99/65915. However, a reproducible and consistent method for the preparation of Form I with chirally pure material (ee >99%) was in doubt since chiral purity of the material (Clopidogrel bisulfate) with m.p. 184 ± 3 °C, disclosed in U.S. Patent 4,847,265 was not precisely known (degree of imprecision 4 % as discussed above.).

In fact, we have observed that formation of Form I of (*S*)-(+)-Clopidogrel bisulfate with chiral purity >99% ee) is inconsistent and difficult to reproduce using the procedures reported in U.S. Patent 4,847,265 and WO 99/65915 whereas the formation of Form II is extremely facile and consistent with optically pure (*S*)-(+)-Clopidogrel free base.

We have disclosed improved processes for the manufacture of (*S*)-(+)- Clopidogrel bisulfate [Indian Patent Applications 84/MUM/2001 (WO 02059128, US 6635763); 335/MUM/2001 and 630/MUM/2001] which are cited herein in their entirety as reference.

We have also disclosed amorphous form of (*S*)-(+)- Clopidogrel bisulfate as hydrates/containing 1-3% water, solvates (methanolates, ethanolates), containing different form stabilizers and process for their preparation [Indian Patent Applications 1190/MUM/2001 & PCT/IN03/00053].

We have also disclosed in this application mixtures of amorphous Clopidogrel bisulfate and Form I and amorphous Clopidogrel bisulfate and Form II which is also cited herein in its entirety as reference.

Amorphous Clopidogrel bisulfate and other solvated forms (1-butanol, 2-butanol, isopropanol, 1-propanol) as well mixtures of amorphous form and Form I & Form II and processes for preparing them have been disclosed in Teva's application no. WO 03/051362 A2, which is cited herein as reference. However, this application does not disclose amorphous Clopidogrel bisulfate hydrate, as well as amorphous Clopidogrel bisulfate containing form stabilizers like PEG or amorphous Clopidogrel bisulfate as methanolates or ethanolates

Teva's application also discloses process for preparing Form I & Form II of Clopidogrel bisulfate. The Form I is prepared by contacting the amorphous form disclosed therein in ethers preferably diethyl ether or MTBE. This process has the following disadvantages:

i. Diethyl ether & MTBE are volatile & inflammable hence are hazardous to work with;
ii. Diethyl ether is very difficult to recover and forms peroxides which are hazardous;
iii. The process cannot be scaled up to plant scale;
iv. Problem of recovery of antisolvents further making the process economically unfeasable.

We herein disclose improved processes for preparing Form I of Clopidogrel bisulfate, with high optical purity (upto ee >99%).

OBJECTIVES OF THE INVENTION

Accordingly, the present invention provides improved processes for preparation of Form I of *(S)*-(+)-Clopidogrel bisulfate.

Another objective of the present invention is to provide a process for preparing Form I of *(S)*-(+)-Clopidogrel bisulfate from different crystalline forms (Form II, III, IV, V, VI or any other forms) or from an oily form of *(S)*-(+)-Clopidogrel bisulfate.

A further objective is to develop improved processes for the preparation of Form I of *(S)*-(+)-Clopidogrel bisulfate from different forms of amorphous Clopidogrel bisulfate including hydrate.

Yet another objective is to develop improved processes for preparation of Form I of *(S)*-(+)-Clopidogrel bisulfate from Clopidogrel base. These processes are easy to scale up, commercially viable, safe, easy to handle and provides operational simplicity.

DESCRIPTION OF INVENTION

The present invention provides improved processes for the preparation of Form I of Clopidogrel bisulfate as described else where in the specification. The term Clopidogrel base, Clopidogrel bisulfate used in the specification means *(S)*-(+)-Clopidogrel base & *(S)*-(+)-Clopidogrel bisulfate.

The Form I can be prepared by any of the processes described below either alone or used in combination.

i) Clopidogrel base in suitable solvents selected from C_5-C_{12} alcohols is treated with dil. H_2SO_4, to obtain Form I of *(S)*-(+)-Clopidogrel bisulfate. Suitable solvents can be selected from C_5-C_{12} alcohols which may be linear or branched, primary, secondary or tertiary alcohols such as pentanol, 2-pentanol, 3-pentanol, isopentanol, hexanol, 2-hexanol, 3-hexanol, isohexanol, heptanol, 2-heptanol, 3-heptanol, 4-heptanol, octanol, isooctanol, decanol, and the like or mixtures thereof.

ii) Clopidogrel base in suitable solvents selected from C_5-C_{12} alcohols and a trace of water is treated with 98 % H_2SO_4, to obtain Form I of *(S)*-(+)-Clopidogrel bisulfate Suitable solvents can be selected from C_5-C_{12} alcohols which may be linear or branched, primary, secondary or tertiary alcohols such as pentanol, 2-pentanol, 3-pentanol, isopentanol, hexanol, 2-hexanol, 3-hexanol, isohexanol, heptanol, 2-heptanol, 3-heptanol, 4-heptanol, octanol, isooctanol, decanol, and the like or mixtures thereof.

iii) Clopidogrel bisulfate in any form including crystalline forms II, III, IV, V, VI or amorphous form or in the form of oil is dissolved/contacted with suitable solvents selected from C_5-C_{12} alcohols to obtain Form I of *(S)*-(+)-Clopidogrel bisulfate. Suitable solvents can be selected from C_5-C_{12} alcohols which may be linear or branched, primary, secondary or tertiary alcohols such as pentanol, 2-pentanol, 3-pentanol, isopentanol, hexanol, 2-hexanol, 3-hexanol, isohexanol, heptanol, 2-heptanol, 3-heptanol, 4-heptanol, octanol, isooctanol, decanol, and the like or mixtures thereof.

iv) Clopidogrel bisulfate in any form including crystalline forms II, III, IV, V, VI or amorphous form or in the form of oil is dissolved/contacted with suitable solvents selected from C_5-C_{12} alcohols and a trace of water, to obtain Form I of *(S)*-(+)-Clopidogrel bisulfate. Suitable solvents can be selected from C_5-C_{12} alcohols which may be linear or branched, primary, secondary or tertiary alcohols such as pentanol, 2-

pentanol, 3-pentanol, isopentanol, hexanol, 2-hexanol, 3-hexanol, isohexanol, heptanol, 2-heptanol, 3-heptanol, 4-heptanol, octanol, isooctanol, decanol, and the like or mixtures thereof.

v) Clopidogrel camphor-sulfonate in suitable solvents like dichloromethane, dichloroethane, chloroform and the like and water is treated with suitable bases, to obtain Clopidogrel base which is then treated with dil. H_2SO_4 in suitable solvents, selected from C_5-C_{12} alcohols to obtain Form I of *(S)*-(+)-Clopidogrel bisulfate. Suitable bases can be selected from NaOH, KOH, LiOH, $NaHCO_3$, Na_2CO_3, K_2CO_3 and the like. Suitable solvents can be selected from C_5-C_{12} alcohols which may be linear or branched, primary, secondary or tertiary alcohols such as pentanol, 2-pentanol, 3-pentanol, isopentanol, hexanol, 2-hexanol, 3-hexanol, isohexanol, heptanol, 2-heptanol, 3-heptanol, 4-heptanol, octanol, isooctanol, decanol, and the like or mixtures thereof.

vi) Clopidogrel camphor-sulfonate in suitable solvents like dichloromethane, dichloroethane, chloroform and the like and water is treated with suitable bases, to obtain Clopidogrel base which is then treated with 98 % H_2SO_4 in suitable solvents, selected from C_5-C_{12} alcohols and a trace of water to obtain Form I of *(S)*-(+)-Clopidogrel bisulfate. Suitable bases can be selected from NaOH, KOH, LiOH, $NaHCO_3$, Na_2CO_3, K_2CO_3 and the like. Suitable solvents can be selected from C_5-C_{12} alcohols which may be linear or branched, primary, secondary or tertiary alcohols such as pentanol, 2-pentanol, 3-pentanol, isopentanol, hexanol, 2-hexanol, 3-hexanol, isohexanol, heptanol, 2-heptanol, 3-heptanol, 4-heptanol, octanol, isooctanol, decanol, and the like or mixtures thereof.

Alternatively, the processes [(i)-(vi)] described above can be repeated by using the Clopidogrel base, Clopidogrel bisulfate and Clopidogrel camphor-sulfonate prepared according to the improved process described by the applicant in US 6635763.

The processes for preparing Form I of (*S*)-(+)-Clopidogrel bisulfate according to the present invention are

- not hazardous as it does not use volatile chemicals like ethers.
- scalable at plant level and so industrially useful
- easy to operate
- good recovery of solvents
- gives high yield of Form I of (*S*)-(+)-Clopidogrel bisulfate

The Form I of (*S*)-(+)-Clopidogrel bisulfate prepared according to the processes of the present invention can be formulated into pharmaceutically acceptable dosage forms by processes known in the art and may be used as an antiplatelet agent.

Dated this 24th day of November 2003

Signature

Dr. B. B. Lohray
(President, Zydus Research Centre)
For Cadila Healthcare Limited

To
The Controller of Patents
The Patent Office, at Mumbai

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